

<b>GlaxoSmithKline</b>	<b>GSK835726</b>
<b>Mechanism of Action</b>	<p>Histamine H1/H3 receptor antagonist</p> <p><a href="http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=262&amp;familyId=33">http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=262&amp;familyId=33</a>  <a href="http://iuphar-db.org/DATABASE/ObjectDisplayForward?familyId=33&amp;objectId=264">http://iuphar-db.org/DATABASE/ObjectDisplayForward?familyId=33&amp;objectId=264</a>  <a href="http://www.ncbi.nlm.nih.gov/gene/3269">http://www.ncbi.nlm.nih.gov/gene/3269</a>; <a href="http://www.ncbi.nlm.nih.gov/gene/11255">http://www.ncbi.nlm.nih.gov/gene/11255</a></p>
<b>Overview</b>	<p>GSK835726 is a potent and selective orally active dual H1/H3 receptor antagonist with a profile consistent with once-daily clinical dosing and has a duration of action that is principally dictated by its pharmacokinetic profile. Potent and selective in Ca<sup>2+</sup> mobilization studies in CHO hH1 (pA<sub>2</sub> = 8.1) and CHO hH3 (pA<sub>2</sub> = 7.8) cells. Selective vs. hH2 or hH4 receptors (both pIC<sub>50</sub> &lt; 5.0). GSK835726 is also a potent antagonist in vitro at endogenous H1 receptors in guinea pig ileum (pA<sub>2</sub> = 7.9) and human bronchus (pA<sub>2</sub> = 7.2) and endogenous H3 receptors in guinea pig ileum (pA<sub>2</sub> = 7.3). GSK835726 has been shown to antagonize H3 receptor mediated inhibition of sympathetically-mediated responses in pig nasal isolated mucosa.</p> <p>Brain penetration was limited in rats following intravenous administration.</p> <p>Oral and IV doses competitively antagonized histamine-induced bronchoconstriction and dermal wheal and flare responses in guinea pigs. Blocked histamine-induced nasal fluid production in pigs when administered prior to intranasal histamine challenge.</p>
<b>Safety/Tolerability</b>	<p>The principal toxicological changes seen in repeat dosing studies were morbidity and mortality at high doses in the dog , rat (over 4 weeks) and mouse (over two weeks). Genotoxicity assessments suggest that GSK835726 does not present a genotoxic hazard to humans. There were no significant safety pharmacology findings of concern for clinical use. Reproductive toxicity studies revealed no evidence of potential for effects on female fertility, early embryonic development or the developing fetus.</p> <p>No adverse effects were noted in preclinical reproduction studies designed to support the use in women of child-bearing potential.</p> <p>In humans, GSK835726 was well tolerated when administered orally in single dose (up to 100 mg) and repeat dosing (up to 50 mg daily for one week) studies, with high bioavailability and an elimination half life suitable for once-daily dosing.</p>
<b>Additional Information</b>	<p>Wheal and flare data from histamine skin challenge showed H1 antagonist activity similar to currently marketed H1 non-sedating antihistamines. GSK835726 showed excellent H1 antagonist activity in both single dose (10, 50 and 100mg administered 2 hours after allergen challenge) and repeat dose (10mg dosed once-daily for 3 days; last dose administered 1h before allergen challenge) in allergen challenge chamber studies. Findings included reduction in nasal congestion; antagonist activity was comparable to cetirizine.</p>
<b>Suitable for and Exclusions</b>	<p>Maximum duration of dosing supported by toxicity studies: 28 days. Applications related to skin disease are of particular interest since GSK studies indicate significant expression of H3 receptors in human skin yet their functional and/or pathophysiological significance remains unclear.</p>
<b>Clinical Trials</b>	<p><a href="http://clinicaltrials.gov/ct2/results?term=GSK835726">http://clinicaltrials.gov/ct2/results?term=GSK835726</a></p>
<b>Publications</b>	<p><a href="http://www.ncbi.nlm.nih.gov/pubmed?term=GSK835726">http://www.ncbi.nlm.nih.gov/pubmed?term=GSK835726</a>  <a href="http://onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.2009.02074.x/pdf">http://onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.2009.02074.x/pdf</a></p>